Introduction

Thermal analysis technique that delivers extremely sensitive measurements of heat change can be applied on a broad scale with pharmaceutical development. These methods provide unique information relating to thermodynamic data of the system studied. The increasing use of the combined techniques is providing more rapid interpretation of the experimental curves obtained.1-12 The need to measure a range of physical parameters has led to the development of numerous techniques such as thermogravimetry (TGA), derivative thermogravimetry (DTG) and differential thermal analysis (DTA). In pharmaceutical sciences thermal methods of analysis have found important applications.3-10 TGA, in which the change in mass of a sample heated at constant rate is recorded and plotted vs. temperature, is an effective method for studying thermal stability and determination the kinetic parameters of the decomposition of drugs. TGA is an analytical, quantitative and comparative method capable of producing fast and reproducible results. It can be used in the quality control of drugs with a view to improvement of the final product and for the determination of drug quality via the technological parameters. DTA is used for the identification of pharmaceutical and organic compounds.11-17 Telmisartan (TMT), 4-[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl) methyl]-biphenyl-2-carboxylic acid (Figure 1), is an angiotensin II type I receptor blocker. It is widely used in treatment of hypertension.18,19 It inhibits the angiotensin II receptor in a way that the effect of angiotensin II is blocked resulting in a decrease of blood pressure.20 Cilazapril (CPL), (1S,9S)-9-[[1(S)-1-(Ethoxycarbonyl)-3-phenylpropyl] amino] octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1- carboxylic acid (Figure 1), is a potent and specific angiotensin converting enzyme (ACE) inhibitor which lowers peripheral vascular resistance without affecting heart rate. It is used in the treatment of hypertension and congestive heart failure.21,22 It also prevents the reabsorption of sodium and water from renal tubules and decreases the heart flow rate.23,24
belong to different groups of antihypertensive drugs, were chosen for study.

Materials and Methods
Telmistran and Cilazapril were obtained from reference standard department (NODCAR), Egypt. The used drugs have high purity (more than 99%).

Methods
The TGA, DTG and DTA Analysis were made using simultaneous TG-DTA apparatus thermal analyzer (Shimadzu DTG-60H). The experiments were performed between ambient and 1000 °C. The temperature program had a heating rate 10 °C/min. Dry nitrogen at a low rate of 30 ML/min was used as the purge gas. The sample mass was kept in the range of 5 mg. α-Al₂O₃ was used as the reference material. The thermodynamic parameters of decomposition processes of the used drugs namely activation energy (E), enthalpy (ΔH'), entropy (ΔS') and Gibbs free energy change of the decomposition (ΔG') were evaluated graphically by employing the Horowitz-Metzger and Coats-Redfern relations.

Horowitz-Metzger method
For the first order kinetic process, the Horowitz-Metzger equation can be represented as follow:

\[
\log \left[ \frac{W_f}{W_f - W} \right] = \frac{\theta E'}{2.303RT^2} = \log 2.303 \ (1)
\]

Where \( W_f \) was the mass loss at the completion of the decomposition reaction, \( W \) was the mass loss up to temperature \( T \), \( R \) was the gas constant, \( T_s \) was the DTG peak temperature and \( \theta = T - T_s \). A plot of \( \log \left[ \frac{W_f}{(W_f - W)} \right] \) against \( \theta \) would give a straight line and \( E' \) could be calculated from the slope.

Coats-Redfern Method
For the first order kinetic process, the activation energy (E') in J.mol⁻¹ could be calculated from the following equation:

\[
\log \left[ \frac{W_f}{W_f - W} \right] = \frac{\phi E'}{2.303RT^2} - \frac{E'}{2.303RT} \ (2)
\]

Where \( \phi \) was the heating rate. Since 1-2RT / \( E' \) ≥ 1, the plot of the left-hand side of equation (2) against 1/\( T \) would give a straight line. \( E' \) was then calculated from the slope and the Arrhenius constant (A) was obtained from the intercept. The entropy \( \Delta S' \), enthalpy \( \Delta H' \) and free energy \( \Delta G' \) of activation were calculated using the following equations:

\[
\Delta S' = 2.303 \log \left( \frac{Ah}{kT} \right) \ R \ (3)
\]

\[
\Delta H' = E' - RT \ (4)
\]

\[
\Delta G' = H' - T \Delta S' \ (5)
\]

Where \( k \) and \( h \) were the Boltzman and Planck constants, respectively. So the calculated values of \( E' \), \( \Delta S' \), \( \Delta H' \) and \( \Delta G' \) could be obtained.

Results and Discussion
Figures (2, 3) show the TGA, DTG and DTA curves of the TMT and CPL, respectively. Table 1 presents the data concerning the main thermal reactions of the examined compounds. Table 2 gives the corresponding DTA reactions.

Thermal analysis of Telmisartan
The TGA and DTG curves of TMT (Figure 2a) show that the compound is thermally stable up to 262 °C. Between 262 and 712 °C, the TGA curve shows mass losses in two steps, while the DTG curve shows one sharp peak and other broad peak. The first step between 262 and 493 °C, a fast process with a mass loss 54.17% is probably due to the thermal decomposition of the compound with the elimination of biphenyl carboxylic acid (C₁₃H₉O₂) and C₄H₈N₂ groups. The second step between 493 and 712 °C where the mass loss is 45.83% is ascribed to pyrolysis of the compound and the loss of C₁₃H₂₀N₂ molecule (Table 1). The DTA curve of TMT (Figure 2b) shows an endothermic flattened peak with its maximum at 456.63 °C. The main thermal decomposition reaction is endothermic peaks followed by exothermic peaks at 569.27 °C and 610.90 °C may be due to the pyrolysis of the compound. In addition the mentioned peaks, the compound has an endothermic reaction which is not accompanied by weight loss, the reaction has its maximum at 265.84 °C. This reaction is endothermic and may be attributed to melting of the compound. Thermal degradation pattern of TMT was presented in Figure 4a.

Figure 2. Thermal analysis curves (TGA, DTG and DTA) of TMT
Thermal analysis of Cilazapril

The TGA and DTG curves in (Figure 3a) show that CPL is thermally stable up to 140 °C then the thermal decomposition of CPL occurs. These curves also show that the mass loss up to 663 °C begins with a fast process, followed by slow process. The first step, which involves a mass loss of 87.50%, is probably due to the elimination of ethoxycarbonyl, carboxylic, carbonyl, phenylpropyl amino and pyridazino groups. The final loss of 12.50% is ascribed to the pyrolysis of the compound and the loss of C₄H₇ group (Table 1).

The DTA curve of cilazapril (Figure 3b) has a shoulder at the beginning of the first endothermic reaction at 99.65 °C this may be attributed to the partial melting and recrystallization of the compound at 63.21 °C. The endothermic peak at 99.65 °C is due to the melting of the compound. An endothermic peak at 411.19 °C may be due to the decomposition of the compound followed by an exothermic peak at 564.33 °C may be attributed to the pyrolysis of the compound. Thermal degradation pattern of CPL was presented in Figure 4b.

Regarding the thermal stability of the compound, it can be concluded from their decomposition reaction that CPL starts to decompose at lower temperature than TMT. That is, TMT is more thermally stable than CPL.

Table 1. The thermal decomposition reaction of TMT and CPL

<table>
<thead>
<tr>
<th>Drug</th>
<th>First step</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wt.Loss (%)</td>
</tr>
<tr>
<td>TMT</td>
<td>45.83</td>
</tr>
<tr>
<td>CPL</td>
<td>12.50</td>
</tr>
</tbody>
</table>

Table 2. DTA peaks and melting points of TMT and CPL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Endothermic Peaks (°C)</th>
<th>Exothermic Peaks (°C)</th>
<th>DTA Method/°C</th>
<th>Melting Point Apparatus (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT</td>
<td>265.84,456.63</td>
<td>569.27,610.90</td>
<td>265.84</td>
<td>263</td>
</tr>
<tr>
<td>CPL</td>
<td>99.65,411.19</td>
<td>564.33</td>
<td>99.65</td>
<td>98</td>
</tr>
</tbody>
</table>

Kinetics and thermodynamic parameters

There were many methods used for the determination of the kinetic parameters. From these, Horowitz and Metzger and Coats and Redfern were applied (Figure 5).

Table 3 shows that the activation energy values (E') of TMT are higher than that of CPL. This conclusion is in accordance with previous conclusion for the thermal decomposition reaction of the compounds. The first reaction of CPL needs lower activation energy and hence the compound is the less stable and starts to decompose first.
Table 3. Thermodynamic parameters of the thermal decomposition of TMT and CPL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Temperature range (°C)</th>
<th>$\bar{E}$ (kJ/mol)</th>
<th>$A$ ($S^{-1}$)</th>
<th>$\Delta S^*$ (kJ/mol K)</th>
<th>$\Delta H^*$ (kJ/mol)</th>
<th>$\Delta G^*$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT</td>
<td>262-493</td>
<td>86.50 (99.27)</td>
<td>1.06 X10^5</td>
<td>(-110.49)</td>
<td>90.60</td>
<td>132.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95.87)</td>
<td>(148.17)</td>
</tr>
<tr>
<td>CPL</td>
<td>140-472</td>
<td>50.82 (63.65)</td>
<td>4.88X10^2</td>
<td>(-154.1)</td>
<td>52.63</td>
<td>92.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(61.26)</td>
<td>(110.50)</td>
</tr>
</tbody>
</table>

Conclusion
The studied compounds TMT and CPL are characterized by having main decomposition reaction and consist of two stages. Besides stability studies, thermal analysis is of value for determining melting temperatures, and water content. The use of clean techniques, and the speed and the simplicity of the analytical methods applied to obtain the results are the reasons behind the even growing importance of thermal analysis in the quality control of active ingredients for medication.

Acknowledgements
The authors extend their appreciation to the National Organization for Drug Control and Research for enabled the possibilities and devices to accomplish this work. Also our greetings to the soul of our Professor doctor Mohamed Elries.

Conflict of Interest
The authors declare that they have no conflict of interest.

References
Thermal decomposition of Telmisartan and Cilazapril